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Impact of Obstructive Sleep Apnea and Continuous Positive Airway Pressure Therapy on Outcomes in Patients with Atrial Fibrillation – Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)

Short title: Impact of OSA on Outcomes in Patients with AF

RCT# NCT01165710

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Abstract

Background: Obstructive sleep apnea (OSA) is common in patients with atrial fibrillation (AF).

Little is known about the impact of OSA on AF treatment and long-term outcomes. We studied whether OSA patients have a greater likelihood of progressing to more persistent forms of AF; require more hospitalizations and/or worse outcomes compared with patients without OSA.

Methods: 10,132 patients were enrolled between 06/2010 and 08/2011 in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) and followed for up to two years. The prevalence of OSA and CPAP treatment was captured at baseline. The association between OSA and major cardiovascular outcomes was analyzed using multivariable hierarchical logistic regression modeling and Cox frailty regression model.

Results: Of 10,132 patients with AF, 1,841 had OSA. OSA patients were more symptomatic (22 vs. 16% severe/disabling symptoms, $P<0.0001$) and more often on rhythm control therapy (35 vs. 31%, $P=0.0037$). In adjusted analyses, OSA patients had higher risk of hospitalization ([HR, 95% CI]: 1.12, 1.03-1.22, $P=0.0078$), but no difference in the risks of death (0.94, 0.77-1.15, $P=0.54$), the composite of CV death, myocardial infarction and stroke/TIA (1.07, 0.85-1.34, $P=0.57$), major bleeding (1.18, 0.96-1.46, $P=0.11$); or AF progression (1.06, 0.89-1.28, $P=0.51$). Patients with OSA on CPAP treatment were less likely to progress to more permanent forms of AF compared with patients without CPAP (0.66, 0.46-0.94, $P=0.021$).

Conclusion: Compared with those without, AF patients with obstructive sleep apnea have worse symptoms and higher risks of hospitalization, but similar mortality, major adverse cardiovascular outcome and AF progression rates.

Clinical Trial Registration: NCT01165710 (<http://www.clinicaltrials.gov>)

Introduction

Obstructive sleep apnea (OSA) has been shown to be independently associated with increased cardiovascular morbidity, including hypertension, congestive heart failure, ischemic heart disease and stroke.¹⁻³ Patients with OSA have a higher prevalence of atrial fibrillation (AF) than patients without OSA,⁴⁻⁷ and patients with OSA are more likely to develop new-onset AF, independent of obesity.⁷ OSA is also associated with an increased risk of AF following coronary bypass surgery, higher recurrence rates of AF following cardioversion, and higher relapse rates of AF after AF catheter ablation.⁸⁻¹⁶

Although patients with OSA have been shown to have higher rates of cardiovascular morbidity than patients without OSA,^{1,2} whether ambulatory patients with AF and OSA experience greater AF progression or worse outcomes than those without OSA remains unknown. Furthermore, although preliminary data indicate that continuous positive airway pressure (CPAP) treatment may be associated with lower recurrence rates of AF post cardioversion,¹⁴ the broader impact of CPAP treatment on outcomes in patients with AF is largely unknown. Therefore the objectives of the current study were: (1) to define the frequency of diagnosed OSA among a nationwide AF population; (2) to determine whether OSA is associated with worse outcomes including hospitalizations, AF complications and survival; (3) to characterize whether OSA is associated with arrhythmic progression of AF and (4) to determine whether or not CPAP treatment is associated with outcomes in patients with AF and OSA.

Methods

The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) is a contemporary registry of outpatients in the US with AF. Its design has been described in detail elsewhere.¹⁷ In brief, a nationally representative sample of sites was invited to participate and an

adaptive design was used to ensure provider and geographic heterogeneity. Consecutive patients with AF meeting the inclusion criteria (at least 18 years of age, electrocardiographic evidence of AF, providing informed consent) and none of the exclusion criteria (life expectancy of less than six months or AF secondary to reversible conditions) were enrolled.

Data collection included demographics, past medical history, type of AF and prior interventions, ongoing antithrombotic therapy, vital signs, laboratory studies, electrocardiographic and echocardiographic findings. The prevalence of clinician defined OSA (i.e., diagnosis or history of OSA) at baseline and CPAP treatment (“currently undergoing CPAP therapy”) was captured. In ORBIT-AF, follow-up data collection occurs at six-month intervals for a minimum of two years. Two-year outcomes were analyzed in this cohort study.

Paroxysmal AF was defined as recurrent AF episodes that terminate spontaneously within seven days; persistent AF as recurrent AF that is sustained for more than seven days; permanent AF was defined as AF in which the presence of the AF is accepted.¹⁸ Progression in AF type was considered as a binary outcome (either ‘the same/better’ or ‘worsening’); worsening was defined as (1) paroxysmal AF at baseline (or ‘first detected/new onset’ AF becoming paroxysmal AF at next available follow-up) becoming persistent or permanent at the last follow-up visit or (2) persistent AF at baseline (or ‘first detected/new onset’ AF becoming persistent AF at next available follow-up) becoming permanent at the last follow-up visit.¹⁹

The baseline ORBIT-AF population included 10,132 patients enrolled between June 2010 and August 2011 from 176 sites. Data on CPAP treatment was lacking in four patients, yielding a study population of 1,837 patients with OSA for the analyses regarding CPAP. For the outcomes analysis for OSA patients vs. no OSA patients, patients without any follow-up data were excluded (n=490). For the outcomes analysis for CPAP treatment vs. no CPAP treatment,

patients without any follow-up data (n=78) and patients from sites with less than 6 patients were excluded (n=135) from the analysis. Sites with less than 6 patients were excluded since these sites had too little information to make within-site comparisons and therefore caused model convergence problems. The exclusion was necessary for the adjusted analysis and was implemented in the unadjusted analysis as well, for consistency. Data are presented as frequencies and percentages for categorical variables and medians (interquartile range) for continuous variables. Groups are compared using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

To examine both the unadjusted and adjusted association between OSA and each of the four outcomes (all-cause death; 1st all-cause hospitalization; the composite of 1st event of cardiovascular death, stroke/non-CNS embolism, TIA or myocardial infarction; 1st major bleed) within two years of baseline enrollment in the registry, a multivariable Cox frailty regression model which accounts for the variability in outcomes between sites was used. For each outcome, backward selection with stay criteria of $P < 0.05$ for candidate variables a pre-specified candidate variable list was performed on the first imputed dataset to construct the Cox frailty regression model. All continuous variables were evaluated for non-linearity with the outcome, and those that did not meet the linear relationship criteria ($P < 0.05$) were accounted for using linear splines. Missing data were multiply-imputed and final estimates and standard errors reflect the combined analysis over five imputed datasets. For AF progression, a multivariable hierarchical logistic regression model was fit including site as a random effect. The same model construction method described for the aforementioned outcomes was used to construct the model for AF progression. Hazard ratio/odds ratio (HR/OR) with corresponding 95% CI and P value are presented.

To explore the CPAP treatment effect in OSA on outcomes, the treatment effect was adjusted for treatment selection bias via propensity score stratification. The predicted probability

of receiving treatment for individuals, given their patient characteristics and site participation was obtained. Since site was included as a fixed effect to obtain the propensity scores, we excluded patients from small sites (patients from sites with less than six patients) from the analysis in order to obtain stable estimates. The propensity scores were then stratified into quintiles. These quintiles formed strata in the final Cox proportional hazard model that accounted for variability in outcomes between sites for all the outcomes except AF progression. Since AF progression was a binary outcome, the quintiles formed strata in a logistic regression model that was fit by generalized estimating equations with a compound symmetric correlation structure to reflect clustering within sites. Both unadjusted and adjusted HR/OR were obtained using methods to account for clustering within sites. Corresponding 95% CI and P value are presented for the association between CPAP and outcomes. The list of candidate variables for all analyzed outcomes is provided in the **Appendix**.

All statistical analyses of the aggregate, de-identified data were performed by the Duke Clinical Research Institute using SAS software (version 9.3, SAS Institute, Cary, NC). All P values were two sided. The Duke Clinical Research Institute was the central coordinating and statistical center for the ORBIT-AF registry, to which de-identified data were sent from the sponsor for statistical analysis. The ORBIT-AF Registry is approved by the Duke Institutional Review Board (approval number Pro00017596), and all participating sites obtained institutional review board approval pursuant to local requirements. All subjects provided written, informed consent.

Sources of Funding

The ORBIT-AF registry is sponsored by Janssen Scientific Affairs, LLC, Raritan, NJ.

Results

Of 10,132 patients enrolled in ORBIT-AF, 18% (n=1,841) had OSA at baseline. **Table 1** shows the baseline characteristics overall and by the presence of OSA. Patients with OSA were younger (69 [62-77] vs. 76 [68-82] years, $P<0.0001$), more often male (69 vs. 55%, $P<0.0001$) and had more comorbidities than patients without OSA, including a greater frequency of a history of heart failure, hypertension, diabetes and hyperlipidemia. Patients with OSA were more likely to have a history of smoking and had a higher prevalence of chronic obstructive pulmonary disease. The body mass index (BMI) of patients with OSA was higher than in patients without OSA (34 [29-40] vs. 28 [25-32] kg/m^2 , $P<0.0001$), their left atria larger (left atrial diameter 4.6 [4.1-5.1] vs. 4.4 [3.9-5.0] cm, $P<0.0001$) and the diastolic blood pressure higher.

Table 2 summarizes the baseline AF characteristics. Patients with OSA were more symptomatic than patients without OSA (22 vs. 16% with severe or disabling symptoms, $P<0.0001$). Patients with OSA were more frequently managed with a rhythm-control strategy (35 vs. 31%, $P=0.0037$) and consequently were more frequently taking an antiarrhythmic drug (33 vs. 28%, $P<0.0001$). They were also more likely to have a history of prior cardioversion (38 vs. 28%, $P<0.0001$). There was no difference in the percentage of patients with or without OSA in sinus rhythm on baseline ECG (34 vs. 33%, $P=0.93$). Despite similar CHADS₂ score, patients with OSA were more often receiving anticoagulation prophylaxis at baseline (79 vs. 75%, $P=0.0020$).

Table 3 summarizes the associations between the outcome variables and OSA. Patients with OSA had higher risk of hospitalization during two-year follow-up (43 vs. 35 events/100 patient-years during follow-up among patients without OSA; adjusted HR 1.12, 95% CI 1.03-1.22, $P=0.0078$). In contrast, the risk of death and the composite of cardiovascular death, myocardial

infarction and stroke/TIA as well as major bleeding were similar in both groups. During follow-up, AF progression occurred in 221 (18% of patients with non-permanent AF at baseline) of the patients with OSA and 984 (18%) of the patients without OSA (adjusted HR 1.06, 95% CI 0.89-1.28, $P=0.51$).

Table 4 and **Figure 1** summarizes the associations between the outcome variables and CPAP treatment in patients with OSA. Of the patients with OSA, 1,067 (58%) were treated with CPAP. Patients with CPAP treatment were younger (68 [62-76] vs. 71 [64-78] years, $P<0.0001$), more often male (72 vs. 64%, $P=0.0004$) and had a higher BMI (36 [31-41] vs. 32 [28-38] kg/m², $P<0.0001$) than patients without CPAP treatment. Furthermore, they more often had diabetes mellitus (44 vs. 39%, $P=0.043$), but the prevalence of valvular disease was lower (20 vs. 24%, $P=0.042$).

In unadjusted and adjusted analyses of patients with OSA, no significant difference in risk was observed between patients on CPAP treatment compared to those not on CPAP for most of the outcomes. The one exception was that a smaller proportion of the patients on CPAP treatment progressed in their AF (16% of patients with non-permanent AF at baseline) compared with the patients not on CPAP treatment (18%; adjusted HR 0.66, 95% CI 0.46-0.94, $P=0.021$).

Discussion

Nearly one in five AF patients in ORBIT-AF carries a diagnosis of OSA. Patients with OSA have worse functional status and slightly higher risks of hospitalization, but similar rates of mortality, AF progression and major adverse cardiovascular events as patients without OSA. No major differences in hospitalization or cardiovascular outcomes were observed between OSA patients

with or without CPAP treatment; however, AF progression was less common in patients treated with CPAP.

Although a large proportion of patients in ORBIT-AF had diagnosed OSA, the observed 18% is substantially lower than reported in some of the previously published literature on both AF and non-AF populations.⁶ This may reflect the fact that ORBIT-AF relies entirely on a history of previously diagnosed OSA; the true prevalence may well have been higher if all patients had been screened with standardized criteria or routine polysomnography. However, it is also possible that the observed prevalence in the ORBIT-AF population more accurately reflects a community-based unselected AF patient population. Not surprisingly, patients with OSA in the current study were more frequently male and had a substantially higher BMI than patients without OSA, consistent with the known major risk factors for OSA.^{5,20} In addition, a higher prevalence of several diseases (e.g., hypertension, congestive heart failure and diabetes) was seen in patients with OSA, compatible with the previously described increased prevalence of cardiovascular diseases in patients with OSA.^{1,2,21}

Patients with AF have an increased risk of OSA and vice versa.⁴⁻⁷ Although OSA and AF have many common risk factors, OSA is an important predictor of new-onset AF, independent of comorbid conditions including obesity.^{7,22} Similarly, obesity alone is associated with a higher risk of AF progression (paroxysmal to permanent).²² Moreover, OSA has also been shown to be associated with more recurrent and symptomatic AF.¹³⁻¹⁶ Indicative of a more 'aggressive' form of AF, patients with OSA in the present study were more symptomatic, had a history of more previous cardioversions and catheter ablations and more often had been or were currently receiving antiarrhythmic drugs and rhythm control strategy. Despite more frequent use of

ablation, antiarrhythmic medications, and the rhythm control strategy there were no differences in the rates of sinus rhythm at baseline or AF progression during follow-up between patients with and without OSA.

Although patients with OSA have been shown to have higher rates of cardiovascular morbidity than patients without OSA,^{1,2} longitudinal outcomes in patients with AF and OSA are lacking. In the current study, patients with OSA did have a higher risk of hospitalization compared with AF patients without OSA. The overall hospitalization rate in ORBIT-AF patients was high (about 48% at two years) and was even higher (almost 54%) in patients with OSA. However, mortality rates and major adverse cardiovascular events and major bleeding were similar to the risk in patients without OSA. Hence, no difference in major adverse cardiovascular events were seen in patients with or without OSA in the current study and a direct causal effect of OSA in cardiovascular disease remains questionable.^{21,23} Similarly, AF did not appear to progress to more persistent/sustained forms more frequently in patients with OSA compared to patients without OSA.

Patients with OSA were more often receiving anticoagulation prophylaxis at baseline in ORBIT AF. This is most likely due to the fact that patients with OSA had more cardiovascular comorbidity (e.g., hypertension and diabetes) and therefore perceived to be at higher risk of stroke, although their lower age and male predominance actually led to similar CHADS₂- and lower CHA₂DS₂-VASc scores.

Apart from behavioral treatment (e.g., weight loss, increased physical activity), CPAP treatment is the most common treatment for moderate-to-severe OSA.²⁴ The rate of CPAP usage in ORBIT AF was 58% with only minor differences in patient characteristics between patients with and

without CPAP treatment. Data on CPAP usage in similar registries are to the best of our knowledge lacking. However, given that CPAP treatment is primarily indicated for treatment of moderate-to-severe OSA and that the adherence to CPAP treatment is known to be low, we believe that 58% of the OSA patients stating that they are “currently undergoing CPAP therapy” seems reasonable. Although several observational studies have indicated that CPAP treatment may be effective in reducing the cardiovascular event-rate in patients with OSA, the observed effect in prospective/randomized studies has at best been modest.^{6,21,25-27} Non-randomized data regarding CPAP treatment of OSA and the likelihood of AF relapse following cardioversion indicate that CPAP is likely beneficial.¹⁴ More recently, specific data regarding CPAP treatment in relation to AF relapse following catheter ablation of AF indicate that CPAP treatment may lower the relapse rate, but randomized comparisons are lacking.¹⁰⁻¹² In keeping with these data, a slightly smaller proportion of patients with OSA on CPAP treatment progressed to more sustained forms of AF in the current study. However, there were no statistically significant differences in mortality rates and major adverse cardiovascular events between patients with OSA treated with CPAP and those without CPAP treatment.

Limitations

These data are from a voluntary, observational study and thus are susceptible to the limitations inherent in such methods. These include both selection and reporting biases. Residual measures and unmeasured confounding may influence these findings. Given that the number of test of primary interest was relatively limited, adjustment for multiple comparisons was not made in order to control Type I error, since this would have increased the risk of Type II error. The diagnosis of OSA in these patients was made based on physician report and medical records. We did not have access to sleep study data, including apnea-hypopnea indices. Likewise, we do not

have data on average duration of CPAP use per night in patients on CPAP treatment. The current study used two-year follow-up. It is possible that the differences between OSA and non-OSA as well as between CPAP treated and non-treated OSA patients would have become more evident over time. On the other hand, our study has several strengths, including a large nationwide cohort with regular follow-up and detailed information on comorbid illness.

Clinical Implications

The frequency of OSA in this nationwide cohort emphasizes the importance of screening for OSA in patients diagnosed with AF. Furthermore, once AF is identified these data highlight the potential role of CPAP as a means to prevent AF progression and decrease AF burden. The role of CPAP in reducing AF burden is currently being evaluated in clinical trials.

Conclusion

Nearly one in five AF patients in our nationally representative cohort study had OSA. Patients with OSA have worse functional status and a higher risk of hospitalization than patients without OSA. However, major adverse cardiovascular events and all-cause mortality did not differ between patients with and without OSA. Similarly, AF in patients with OSA did not appear to progress more frequently to more persistent/sustained forms of AF. In patients with OSA, CPAP treatment may attenuate the rate of AF progression.

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FH had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author contributions: FH, JPP and BJG contributed to the conception and design of the study and to the data analyses and interpretation. NG, ZZ and DNH contributed to the acquisition of data and to data analyses and interpretation. PRK, LAA, GCF, EMH, KWM, JVF, PC and EDP contributed to the conception and design of the study. All authors contributed to preparation of the manuscript and approved the final version. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

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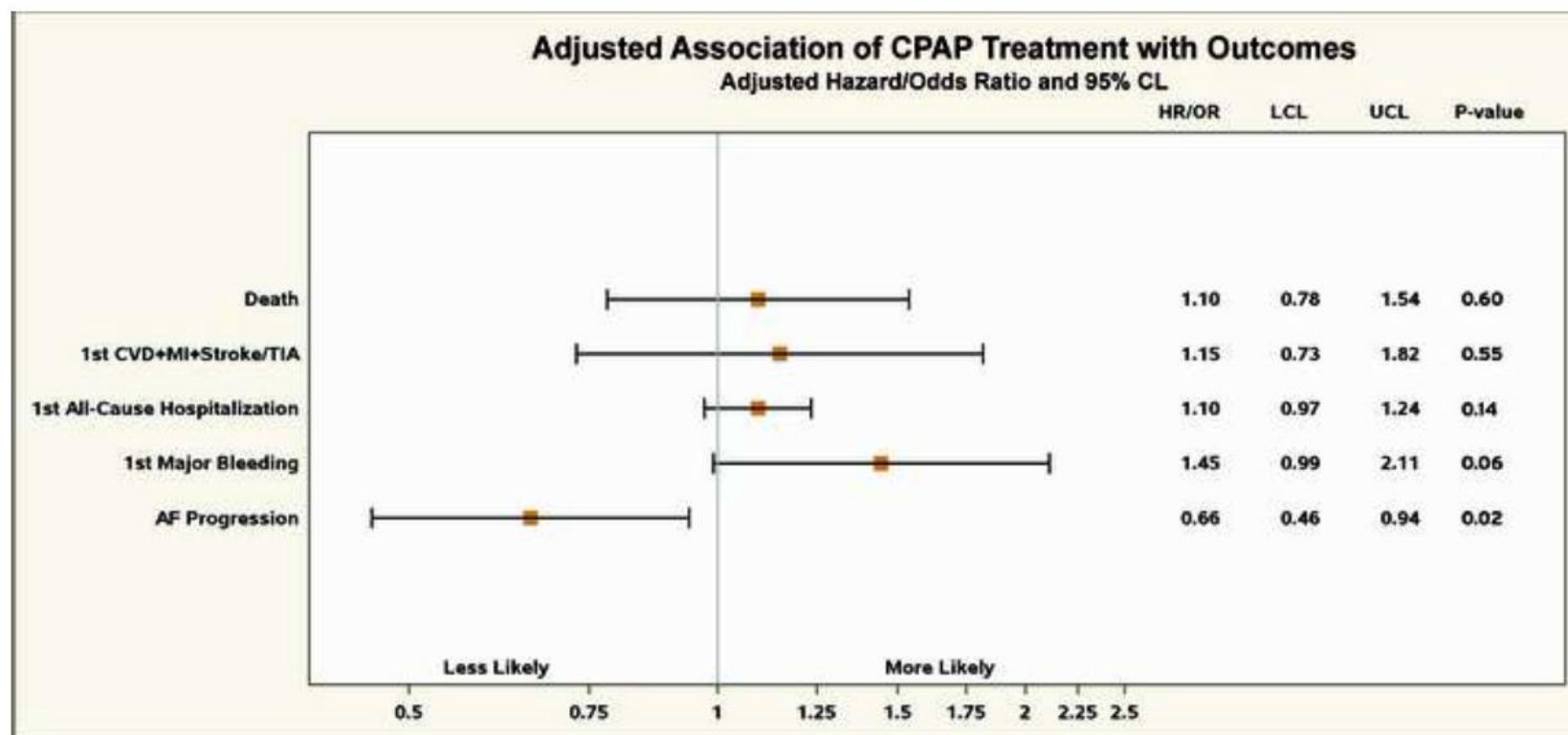


Figure legends*Figure 1*

The figure summarizes the adjusted associations between the outcome variables and CPAP treatment in patients with OSA.

AF = atrial fibrillation; CL = confidence limit; CPAP = continuous positive airway pressure; CVD = cardiovascular death; HR = hazard ratio; LCL = lower confidence limit; MI = myocardial infarction; OR = odds ratio; TIA = transient ischemic attack; UCL = upper confidence limit.

Tables

Table 1 - Baseline Characteristics by Obstructive Sleep Apnea

	Overall (N=10,132)	No OSA (N=8,291)	OSA (N=1,841)	P
Age (years)	75 (67-82)	76 (68-82)	69 (62-77)	<0.0001
Male	58	55	69	<0.0001
Race				
White	89	89	88	0.0004
Black or African-American	5.0	4.6	6.7	
Hispanic	4.2	4.4	3.2	
Other	1.4	1.4	1.5	
Medical History				
Hypertension	83	82	87	<0.0001
Hyperlipidemia	72	71	76	<0.0001
Diabetes	29	27	42	<0.0001
Chronic obstructive pulmonary disease	16	15	25	<0.0001
Prior myocardial infarction	16	16	16	0.69
Heart failure	33	31	40	<0.0001
Valvular disease	25	26	22	0.0002

Peripheral Vascular Disease	13	13	13	0.91
Prior cerebrovascular events	16	16	16	0.76
Stroke (all-cause)	8.9	9.0	8.3	0.36
Non-hemorrhagic	8.0	8.1	7.2	0.21
Hemorrhagic	0.8	0.8	0.8	0.99
Other intracranial bleeding	0.9	1.0	0.8	0.41
Gastrointestinal bleeding	9.0	8.8	10	0.0343
Cognitive impairment or dementia	3.1	3.1	2.9	0.60
Frailty	5.8	6.1	4.3	0.0029
Smoking	48	47	55	<0.0001
Alcohol abuse	4.0	3.7	5.5	0.0004
BMI (kg/m ²)	29 (25-34)	28 (25-32)	34 (29-40)	<0.0001
Systolic blood pressure (mmHg)	126 (116-138)	126 (116-138)	125 (116-136)	0.85
Diastolic blood pressure (mmHg)	72 (66-80)	72 (66-80)	73 (68-80)	0.0033
Left ventricular ejection fraction > 50%	70	70	72	0.96
Left atrial diameter (cm)	4.4 (3.9-5.0)	4.4 (3.9-5.0)	4.6 (4.1-5.1)	<0.0001

Continuous variables are presented as median and inter-quartile range. AF=atrial fibrillation; BMI=body mass index; bpm=beats per minute

Table 2 - Atrial Fibrillation History by Obstructive Sleep Apnea

	Overall (N=10,132)	No OSA (N=8,291)	OSA (N=1,841)	P
AF type				
First detected/new onset	4.7	5.0	3.7	
Paroxysmal	51	51	50	0.043
Persistent	17	17	18	
Permanent	28	28	28	
Family history of AF	15	14	17	0.0091
Duration of AF diagnosis (months)	47 (17-93)	47 (17-94)	46 (18-91)	0.92
Sinus rhythm on most recent ECG	33	33	34	0.93
EHRA symptom level				
No symptoms	38	39	33	<0.0001
Mild	45	45	45	
Severe	15	14	19	
Disabling	1.8	1.7	2.7	
CHADS ₂ risk groups				
0	6.4	6.6	5.3	0.73
1	22	22	23	
≥2	72	72	72	

CHA ₂ DS ₂ -VASc score (mean ± SD)	3.9±1.8	4.0±1.8	3.7±1.8	<0.0001
Prior treatment				
Oral anticoagulation therapy	82	81	85	<0.0001
Antiarrhythmic drug	45	44	52	<0.0001
Prior cardioversions	30	28	38	<0.0001
Prior catheter ablation of AF	5.5	5.0	7.7	<0.0001
Current treatment				
Oral anticoagulation therapy	76	75	79	0.0020
Antiarrhythmic drug	29	28	33	<0.0001
Rhythm strategy	32	31	35	0.0037

Continuous variables are presented as median and inter-quartile range. AF=atrial fibrillation; EHRA=European Heart Rhythm Association

Table 3 - Association of Obstructive Sleep Apnea and 2-year Outcomes

Outcome	OSA	No OSA	Unadjusted		Adjusted HR	
	(n=1,763)	(n=7,879)	HR	P	(95% CI)	P
	# of events	# of events				
	(events/100 patient-years)	(events/100 patient-years)				
All-cause Death	127 (4.45)	672 (5.35)	0.83 (0.68-1.01)	0.057	0.94 (0.77-1.15)	0.54
1 st Hospitalization (All-cause)	866 (43.3)	3,324 (35.0)	1.17 (1.09-1.27)	<0.001	1.12 (1.03-1.22)	0.007
CV death, MI, stroke/TIA	106 (3.77)	494 (3.99)	0.96 (0.75-1.15)	0.51	1.07 (0.85-1.34)	0.57
Major bleeding	123 (4.47)	463 (3.79)	1.18 (0.96-1.44)	0.12	1.18 (0.96-1.46)	0.11
Outcome	OSA	No OSA	Unadjusted OR		Adjusted OR	
	(n = 1,223)	(n = 5,349)	(95% CI)	P	(95% CI)	P
	# of events	# of events				
	(proportion)	(proportion)				
Progression of AF type	221	984	1.05 (0.88-1.24)	0.60	1.06 (0.89-1.28)	0.51

Adjusted hazard ratios (HR) are calculated using Cox frailty models for all outcomes except the association between OSA and progression of AF, where logistic regression was used to calculate the associated odds ratio (OR). AF = atrial fibrillation; CV = cardiovascular; OSA = obstructive sleep apnea; TIA = transient ischemic attack

Table 4 - Association of OSA with and without CPAP treatment and 2-year outcomes

Outcome	CPAP	No CPAP	Unadjusted		Adjusted HR	
	(n=937)	(n=687)	HR		P	
	# of events	# of events	HR		P	
	(events/100 patient-years)	(events/100 patient-years)	(95% CI)		(95% CI)	
All-cause Death	68 (4.44)	54 (4.86)	0.92 (0.67-1.25)	0.58	1.10 (0.78-1.54)	0.60
1 st Hospitalization (All-cause)	471 (43.9)	329 (41.9)	1.05 (0.93-1.18)	0.42	1.10 (0.97-1.24)	0.14
CV death, MI, stroke/TIA	57 (3.78)	41 (3.73)	1.02 (0.68-1.52)	0.94	1.15 (0.73-1.82)	0.55
Major bleeding	71 (4.81)	43 (3.99)	1.20 (0.85-1.71)	0.29	1.45 (0.99-2.11)	0.06
Outcome	CPAP	No CPAP	Unadjusted OR		Adjusted OR	
	(n = 602)	(n=411)	OR		P	
	# of events	# of events	OR		P	
	(proportion)	(proportion)	(95% CI)		(95% CI)	
Progression of AF type	94	75	0.74 (0.55-0.99)	0.04	0.66 (0.46-0.94)	0.02

AF = atrial fibrillation; CPAP = continuous positive airway pressure; CV = cardiovascular; HR = hazard ratio; OSA = obstructive sleep apnea; TIA = transient ischemic attack.